Stereospecific Alkene Aziridination Using a Bifunctional Amino-Reagent: an Aza-Prilezhaev Reaction

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Supporting Information Placeholder

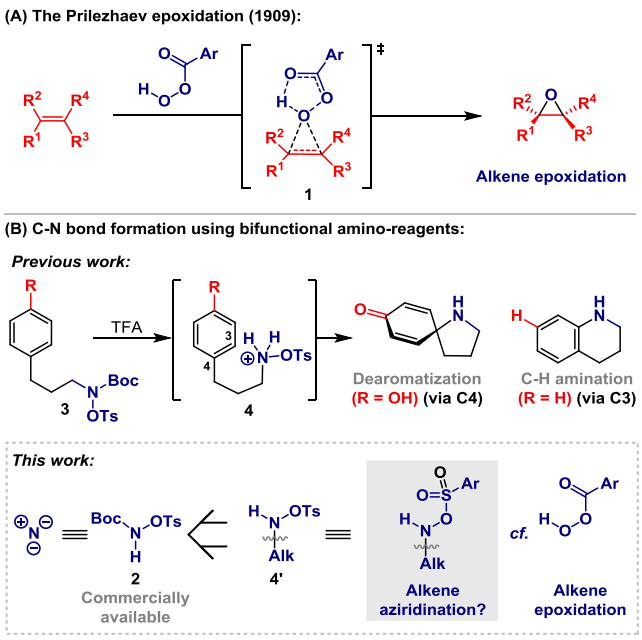
ABSTRACT: In situ deprotection (TFA) of O-Ts activated N-Boc hydroxylamines triggers intramolecular aziridination of N-tethered alkenes to provide complex N-heterocyclic ring systems. Synthetic and computational studies corroborate a diastereospecific aza-Prilezhaev-type mechanism. The feasibility of related intermolecular alkene aziridinations is also demonstrated.

Epoxidations of non-polarized alkenes are commonly achieved by their exposure to peracids, usually *m*-CPBA (Scheme 1A).[1] This process, reported in 1909 by Prilezhaev (Prileschajew), has become a cornerstone reaction of organic chemistry because it is operationally simple and diastereospecific.[2] This latter facet is attributed to a mechanism wherein simultaneous formation of both new C-O bonds occurs via butterfly-like transition state **1**.[3] By contrast, analogous stereospecific alkene aziridinations are virtually unknown; instead, this transformation is typically achieved under mechanistically distinct metal-catalyzed conditions, often involving nitrenoids.[4-7] Although there are exceptions,[5e] such methods can only usually generate aziridines with electron withdrawing groups on nitrogen. The absence of reagents that can promote simple metal-free Prilezhaev-like aziridinations is surprising. Existing metal-free aziridinations of non-polarized alkenes either require strong external oxidants and/or are not stereospecific and/or offer limited flexibility with respect to the nitrogen substituent.[6] Consequently, the provision of a simple and stereospecific alkene aziridination protocol that provides N-alkylated products is a challenging and worthwhile objective.

Recently, we reported that in situ deprotection of O-Ts activated N-Boc hydroxylamines **3** generates a potent electrophilic aminating agent (**4**) that can be harnessed for C-N bond forming dearomatizations or C-H aminations of pendant arenes (Scheme 1B).[8a,9] Key features of these processes include (a) their operational simplicity and (b) direct access to the substrates via Mitsunobu alkylation of commercially available bifunctional amino-reagent **2**.[10] The free base of intermediate **4** (**4'**) has an obvious structural analogy to *m*-CPBA, and this led us to question whether Prilezhaev-like alkene aziridinations might be feasible. In these processes, N-alkylation of reagent **2** would precede alkene aziridination, with the two-step sequence using **2** as a synthetic linchpin equivalent to an "N-+-" synthon. Outlined below is the successful realization of this idea, which provides unique examples of aza-Prilezhaev reactions. Our results offer a counterpoint to established metal-catalyzed alkene aziridinations and provide a framework for the development of a general metal-free protocol.

Our studies commenced by examining the intramolecular aziridination of system **5a** (R^1 = Ph), which contains a *trans*-configured styrene (Table 1A); this was easily accessed by Mitsunobu alkylation of **2** (93% yield; see the SI). Remarkably, exposure of a TFE

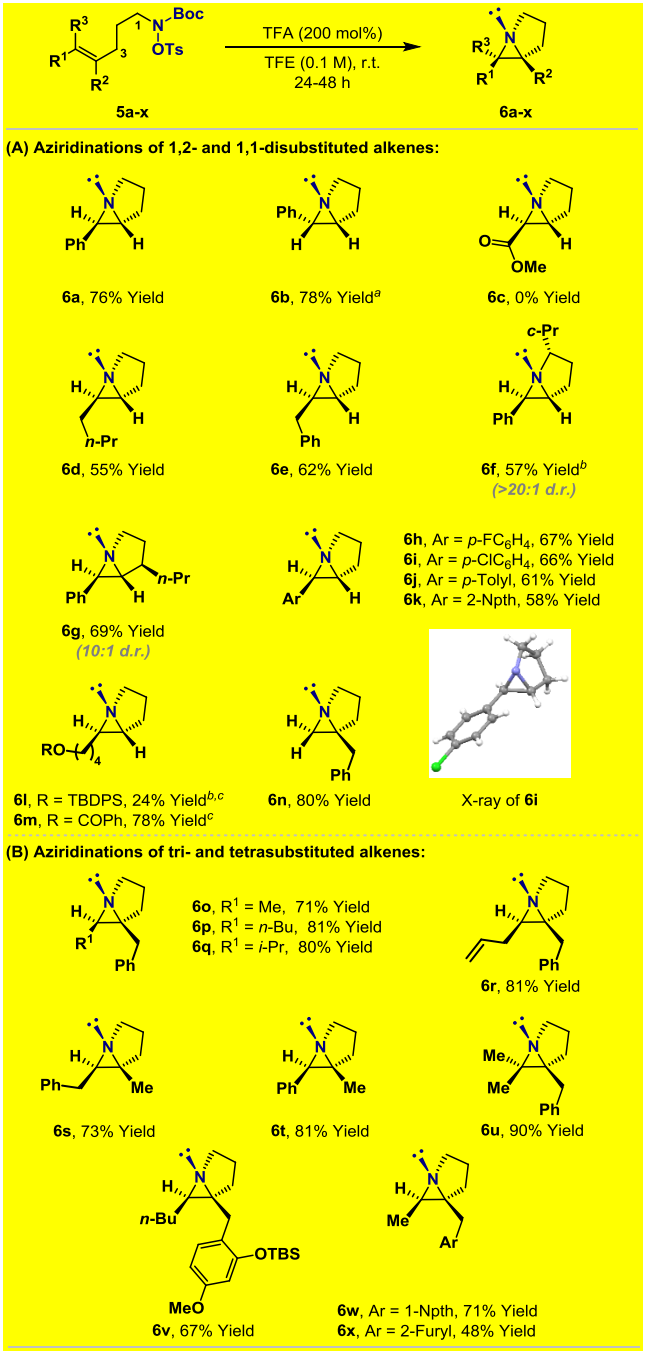
Scheme 1.



solution of **5a** to TFA (200 mol%) resulted in efficient aziridination to provide **6a** in 76% yield and as a single diastereomer. More common alcohols (e.g. EtOH) were not effective solvents, whereas appreciable quantities of **6a** were observed using CH_2Cl_2 (40%) or PhMe (32%) (see the SI). When the corresponding system containing a *cis*-styrene (**5b**, R^3 = Ph) was subjected to the TFE/TFA conditions, aziridine **6b**, the diastereomer of **6a**, was generated as the sole product in 78% yield. Thus, the process is diastereospecific with respect to olefin geometry. Further studies sought to evaluate scope with respect to the alkene. Electron deficient variants do not participate, as evidenced by attempted aziridination of acrylate system **5c**, which did not provide detectable quantities of target **6c**. However, other classes of electron rich alkene are suitable, such that 1,2-dialkylated system **5d** provided **6d** in 55% yield. Extension to a range of styrenes and 1,2- or 1,1-disubstituted alkenes provided products **6e-n** in an efficient manner; the structure of **6i** was confirmed by single crystal X-ray diffraction. Protected alcohols are tolerated, providing the protecting group is relatively stable to acid (cf. **6l** vs **6m**). Systems containing additional substitution at either C1 or C3 undergo highly diastereoselective cyclization, as highlighted by the efficient formation of **6f** and **6g**. For substrates containing very electron rich styrenes, reaction efficiency is compromised by the instability of the aziridine product under the reaction conditions (vide infra); this accounts for the diminished yield in the

conversion of **5k** to **6k**. Classically, bicyclic aziridines related to those described in Table 1 have been accessed by $Pb(OAc)_2$-mediated cyclization of primary amines onto alkenes;[11] the present method offers much wider scope and has the obvious benefit of circumventing the requirement for stoichiometric quantities of a toxic Pb-based reagent.

Table 1. Aziridinations of di-, tri- and tetrasubstituted alkenes.

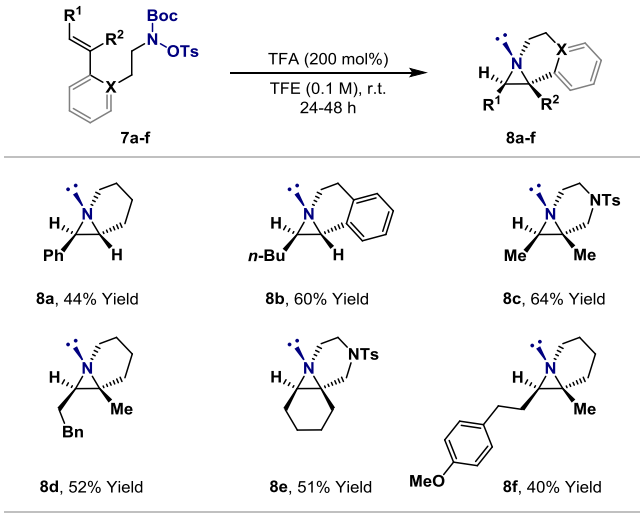


[a] Isolated as the TsOH salt. [b] 72 h. [c] The free alcohol of **5l/m** (R = H) did not undergo efficient aziridination.

A notable feature of the new aziridination protocol is its ability to construct highly substituted aziridines (Table 1B). Cyclizations involving trisubstituted alkenes proceeded smoothly to provide targets **6o-t** and **6v-x** with minimal variation in efficiency. The reaction conditions are sufficiently mild that O-TBS protected phenols remain intact (e.g. **5v** to **6v**) and acid promoted isomerization of skipped dienes (**5r** to **6r**) was not observed. Tetrasubstituted alkenes are also effective reaction partners as evidenced by the formation of **6u**, which occurred in 90% yield. The ability to form highly congested C-N bonds suggests that the method will be of high value in target directed settings, especially alkaloid synthesis.

Although the intramolecular aziridination process is most effective for 5-ring cyclizations, we have also found that 6-ring processes occur with synthetically useful levels of efficiency (Table 2). Cyclization of styrene-based system **7a** was relatively demanding, and **8a** was isolated in 44% yield. Conversely, aziridination to generate benzofused system **8b** was more efficient, occurring in 60% yield. As with 5-ring cyclizations, non-styrenyl alkenes also participate; for example, aziridinations involving acyclic trisubstituted olefins provided **8c**, **8d** and **8f** in modest to good yields. Intramolecular aziridination of a cyclic alkene (**7e**) provided highly complex tricyclic system **8e** in 51% yield.

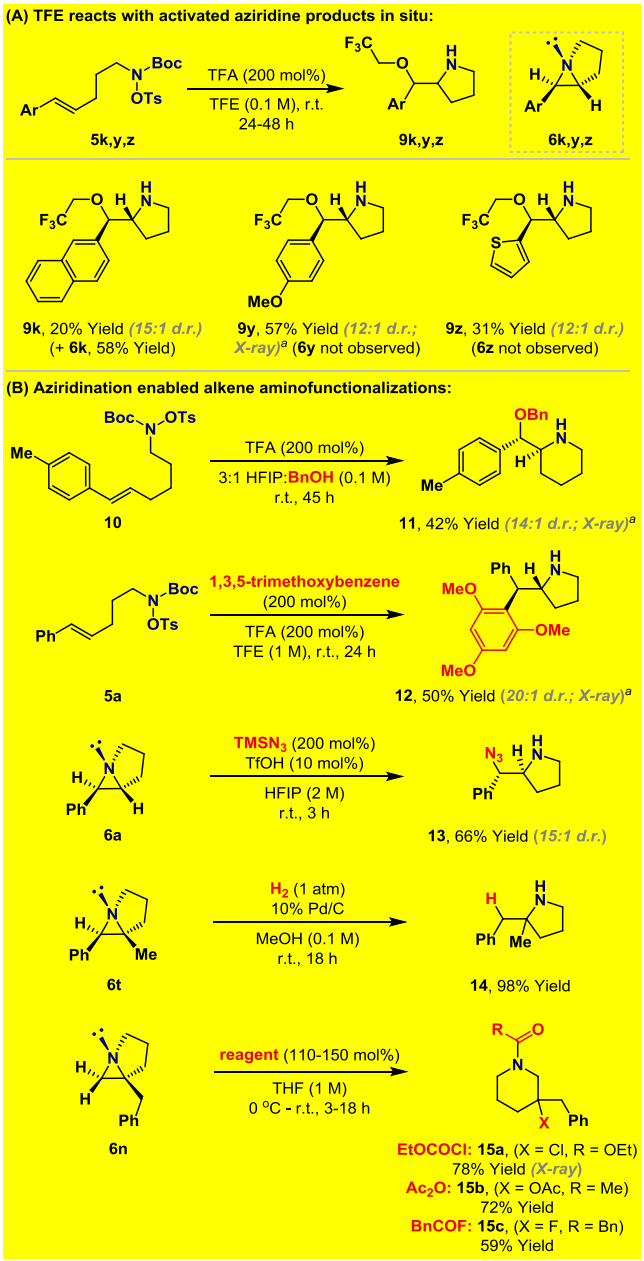
Table 2. Aziridinations to give azabicyclo[4.1.0]heptanes.



As noted earlier, aziridine **6k** was unstable to the reaction conditions with competitive formation of 1,2-aminoetherification product **9k** (15:1 d.r.) observed in 20% yield (Scheme 2A). When **6k** was resubjected to the aziridination conditions **9k** was formed as the sole identifiable product. These observations are consistent with the electron rich naphthyl unit of **6k** facilitating acid promoted ionization of the aziridine to provide a benzylic carbocation, which is captured by TFE in a diastereocontrolled S_N1 reaction.[12] For substrates **5y** and **5z**, which bear highly stabilizing *para*-methoxyphenyl or 2-thienyl substituents, aziridine products **6y** and **6z** were not observed and competing alkene 1,2-aminoetherification products formed exclusively. Attempts to suppress ring opening of the initially formed aziridine by varying the reaction solvent or acid were unsuccessful; in part, this reflects the observation that TFE/TFA is easily the most effective combination found so far for the aziridination process. However, by switching to less nucleophilic HFIP as solvent, we were able to use BnOH as an external nucleophile and this provided 1,2-aminoetherification product **11** in 42% yield (14:1 d.r.) directly from alkene **10**.[13] Based on this, we examined whether the aziridination-ionization sequence could be adapted to other classes of alkene 1,2-difunctionalization (Scheme 2B). Under optimized aziridination conditions, inclusion

of trimethoxybenzene as an exogenous nucleophile enabled the direct conversion of alkene **5a** to 1,2-aminoarylation product **12** in 50% yield and 20:1 d.r.[14] 1,2-Aminoazidation product **13** was accessed by exposing aziridine **6a** to $TMSN_3$ under acidic conditions; in this case, direct conversion of **5a** (the alkene precursor to **6a**) to **13** was less efficient.[15] Formal alkene hydroaminations can be achieved by hydrogenative C-N reduction of benzylic aziridines; for example, **6t** was converted to **14** in 98% yield. Ring expansions to piperidines are facile as evidenced by the efficient conversion of **6n** to **15a-c**.[16] The relative stereochemistries of **9y**, **11**, and **12** were determined by single crystal X-ray diffraction of crystalline derivatives. Stereochemical assignments of **9k** and **9z** are made by analogy, and the assignment of **13** is based on comparison to reported NMR data.

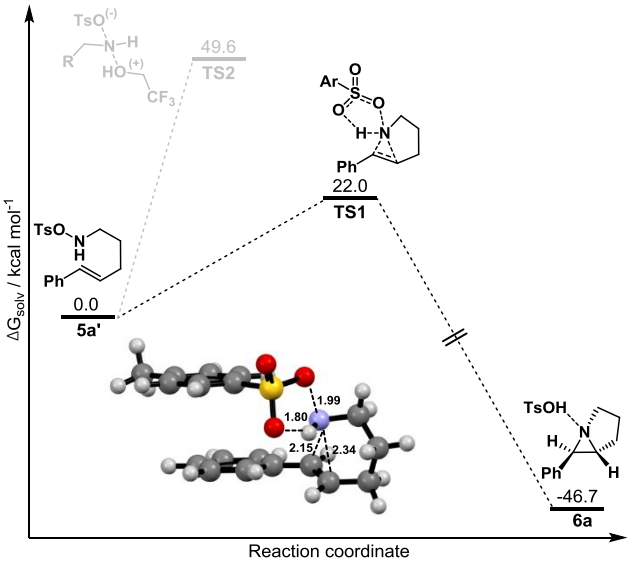
Scheme 2.



[a] An X-ray structure of a derivative was obtained (see the SI).

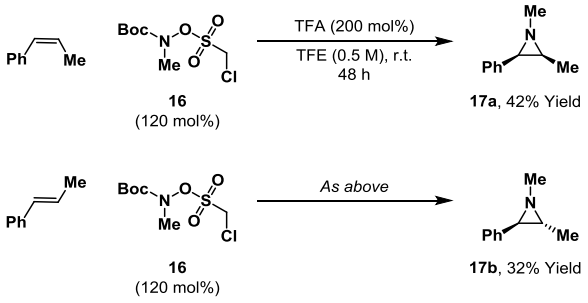
The diastereospecificity of the processes described here (cf. **6a** and **6b**) suggests that, following Boc-deprotection (TFA), alkene aziridination proceeds in a concerted manner, where both new C-N bonds form simultaneously. Mechanistically, this could be rationalized either by the formation and capture of a nitrenium ion or by an aza-Prilezhaev-type mechanism. To our knowledge, efficient alkene aziridinations using nitrenium ions without stabilizing groups are unknown.[17] Indeed, computational studies on the conversion of **5a'** (the Boc-deprotected version of **5a**) to **6a** indicate that formation of a solvent-stabilized nitrenium ion has a large energy barrier (**TS2**, $\Delta G^{\ddagger}$ = 49.6 kcal mol^{-1}) (Figure 1). On the other hand, the transition state for an aza-Prilezhaev pathway (**TS1**) is accessible ($\Delta G^{\ddagger}$ = 22.0 kcal mol^{-1}) and strongly resembles the spiro 'butterfly' transition state involved in *m*-CPBA-mediated alkene epoxidations (see the SI for details).[3,18,19] Thus, in line with our initial reaction design, we favor an aza-Prilezhaev pathway for the processes described here.

Figure 1. Reaction profiles for the generation of a nitrenium ion (grey) and aziridination of 5a' via an aza-Prilezhaev mechanism (black).[a]



[a] Solvated Gibbs free energies are quoted at PBE0/6-311++G(2d,p)//PBE0-D3BJ/6-31+G(d), SMD(TFE). Free energy contributions have been calculated at 298 K. See the SI for details.

Scheme 3. Preliminary intermolecular aziridination results.



Although our focus so far has been on the development of intramolecular aziridinations, we have also validated the method in intermolecular settings (Scheme 3). Exposure of *cis*-β-methylstyrene to reagent **16** (120 mol%) in the presence of TFA delivered *cis*-configured aziridine **17a** as the sole diastereomer in 42% yield.

Similarly, aziridination of *trans*-β-methylstyrene provided *trans*-configured aziridine **17b** in 32% yield. The diastereospecificity of these reactions mirrors observations made earlier, which suggests that an analogous reaction pathway is operative. Notably, the OTs analogue of **16** was not effective for the formation of **17a** and **17b**.[20] Accordingly, modification of the electrophilic nitrogen source can improve reaction efficiency and this provides an avenue for the development of a more general intermolecular protocol; studies towards this objective are ongoing. Notably, N-Me aziridines have previously been prepared by metal-catalyzed nitrenoid transfer from reagents that bear a close similarity to the Boc-deprotected form of **16**;[5e] the results in Scheme 3 highlight the feasibility of a complementary metal-free alternative.

In summary, we show that activated hydroxylamines engage alkenes in a process that resembles an aza-variant of the *m*-CPBA promoted Prilezhaev reaction, a process reported over one hundred years ago. The substrates are easily accessed by Mitsunobu alkylation of commercially available "linchpin" reagent **2**.[21] Intramolecular versions of the aziridination process provide direct access to structurally intriguing N-heterocyclic ring systems. These can be modified further in a distinct step, or harnessed in tandem one-pot processes, as the basis of an approach to alkene 1,2-amino-functionalization. Preliminary studies demonstrate the feasibility of related intermolecular aziridinations. Our studies provide unique examples of transition metal-free *stereospecific* alkene aziridinations that provide N-alkylated products. Efforts to broaden the utility of the process are underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, crystallographic data and computational details including method evaluation and consideration of alternative reaction pathways. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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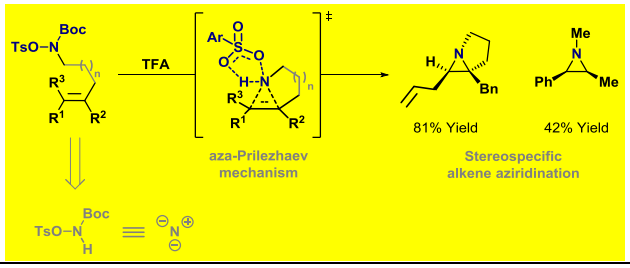
(17) Similar considerations were noted in our earlier work (reference 8a). Reference 6h describes an aziridination protocol that is suggested to proceed via a stabilized nitrenium ion. For other examples, see: (a) Vedejs, E.; Sano, H. Synthesis of N-Methoxy and N-H Aziridines from Alkenes. *Tetrahedron Lett.* **1992**, *33*, 3261; (b) Bowen, E. G.; Wardrop, D. J. Diastereoselective Nitrenium Ion-Mediated Cyclofunctionalization: Total Synthesis of (+)-Castanospermine. *Org. Lett.* **2010**, *12*, 5330.
(18) Although subject to debate, an aza-Prilezhaev like pathway has been invoked for aziridinations promoted by in situ oxidation of N-aminophthalimide: (a) Atkinson, R. S.; Grimshire, M. J.; Kelly, B. J. Aziridination by Oxidative Addition of N-Aminoquinazolones to Alkenes: Evidence for Non-Involvement of N-Nitrenes. *Tetrahedron* **1989**, *45*, 2875; (b) Atkinson, R. S.; Jones, D. W.; Kelly, B. J. Evidence for Phthalimidonitrene as a Common Intermediate in Several Extrusion Reactions. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1344.
(19) Further computational studies are presented in the SI. These studies do not support aziridination via the protonated form of **5a'** or homolysis to generate an N-centered radical. The stereospecific nature of the aziridination process is also not consistent with a radical mechanism.
(20) At the present stage of development, more highly substituted styrenes and non-conjugated alkenes do not participate in intermolecular aziridination.
(21) DSC analyses of compounds **2**, **16** and **OTs-16** are given in the SI. Compounds related to **2** have been used on scale: Mendiola, J.; Rincón, J. A.; Mateos, C.; Soriano, J. F.; de Frutos, O.; Niemeier, J. K.; Davis, E. M. Preparation, Use, and Safety of *O*-Mesitylenesulfonylhydroxylamine. *Org. Process Res. Dev.* **2009**, *13*, 263.


Boc
TsO–N
R3
R1
R2
TFA
Ar
S
O
H–N
aza-Prilezhaev
mechanism
H
N
Bn
81% Yield
Me
N
Ph
Me
42% Yield
Stereospecific
alkene aziridination